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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,763	11/17/2003	Hashem Akhavan-Tafti	N-1-001	3365

67504 7590 05/13/2008

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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
05/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,763	AKHAVAN-TAFTI ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-43,45-48 and 51-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-30,32-43,45-48 and 51-54* is/are rejected.

7)☒ Claim(s) *31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on January 4, 2008 is acknowledged and has been entered. Claims 4 and 43 have been amended. Claims 2, 44 and 49 have been canceled. Claims 51-54 have been added. Claims 1, 3-43, 45-48 and 51-54 are pending.

Claims 1, 3-43, 45-48 and 51-54 are discussed in this Office action.

Applicant's arguments, see p. 14-15, filed January 4, 2008, with respect to the rejection(s) of claim(s) 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 under 35 U.S.C. 103 as being unpatentable over Greenfield in view of Summerton have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made further in view of Warth, Linda (Thesis, UMI, Iowa State University, 1988, p. 70-102, 144-146, 'Warth' herein).

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL in view of the new grounds of rejection.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

1. Claims 1, 3-12, 19-22, 30, 32-35, 42-46 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (US PgPub 2004/0121336; June 2004) as evidenced by Ishikawa et al. (Colloid and Polymer Science, 1984, vol. 262, p. 477-480) in view of Summerton et al. (US Patent 6,060,246; May 2000) and Warth, Linda (Thesis, UMI, Iowa State University, 1988, p. 70-102, 144-146). Greenfield teaches a method for binding a predetermined amount of nucleic acid comprising binding the nucleic acid to solid substrate binding units (Abstract).

With regard to claim 1, Greenfield teaches a method of isolating a nucleic acid from a sample comprising:

a) providing a solid phase comprising a matrix selected from silica, glass, insoluble synthetic polymers, and insoluble polysaccharides (p. 2, paragraph 31, where the support can comprise silica, beads or resin); a nucleic acid binding portion for attracting and non-sequence-specific binding of nucleic acids, wherein the nucleic acid binding portion of the solid phase is selected from a ternary sulfonium group of the formula SR2+X- where R is selected from C1-C20 alkyl, aralkyl and aryl groups, a quaternary ammonium group of formula NR3+X- wherein R is selected from alkyl, aralkyl and aryl groups, and a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and where X is an anion (p. 3, paragraph 31, where the binding component may comprise anion exchange groups such as DEAE or p. 3, paragraph 42, where the anion exchange group refers to tertiary and quaternary amines or see p. 6, paragraph 75, where the exchange resins include QAE , a quaternary

ammonium group, referring specifically to diethyl(2-hydroxypropyl)aminoethyl as evidenced by Ishikawa, p. 477, 'materials and methods'; see also p. 6, paragraph 77, where the binding units can comprise tetramethyl ammonium, tetraethyl ammonium, tetrapropyl ammonium, tetrabutyl ammonium and combinations therein, where these also represent quaternary ammonium groups together with a variety of anions, including chloride and fluoride);

b) combining the solid phase with the sample containing the nucleic acid to bind the nucleic acid to the solid phase (p. 6, paragraph 71, where nucleic acids are bound to the binding units);

c) separating the sample from the solid phase and e) releasing the nucleic acid from the solid phase (p. 6, paragraph 79, where after binding the units are washed and therefore are separated from the original sample and paragraph 71, where the nucleic acids are eluted before being used in an assay).

d) a linker portion linking the nucleic acid binding portion to the solid support (p. 7, paragraph 97; p. 2 paragraph 32).

With regard to claim 6 and 9-10, Greenfield teaches an embodiment of claim 1, wherein the solid support portion is selected from particles, microparticles and beads (p. 2, paragraph 29, where the solid substrate comprises microspheres, spheres, and paragraph 29 where the solid substrate includes beads and resins).

With regard to claim 44, Greenfield teaches an embodiment of claim 1, further comprising, after step b) washing the solid phase having captured nucleic acid bound thereto with a wash solution to remove other components of the sample from the solid phase (p. 6, paragraph 79, where after binding the units are washed to remove components other than the bound nucleic acids).

With regard to claim 48 and 49, Greenfield teaches an embodiment of claim 1 and 2 further comprising: a) releasing the nucleic acid from the solid phase in step e) into a solution; and b) using the solution containing the released nucleic acids directly in a downstream process (p. 6, paragraph 71, where the nucleic acid is eluted and used in a downstream assay, such as PCR, sequencing, restriction analysis, cloning or hybridization); and b) using the solution containing the released nucleic acid directly in a downstream process (p. 6, paragraph 71, where the nucleic acids are eluted before being used in an assay).

Regarding claim 1 and 2, Greenfield does not teach the limitation that the solid phase comprises a cleavable linker portion or cleaving the cleavable linker portion.

Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

With regard to claim 1, Summerton teaches and a cleavable linker portion linking the nucleic acid binding portion to the solid support (col. 7, lines 15-17 and col. 8, line 64 to col. Col. 9, line 42, where the cleavable linker can include disulfide, esters, orthonitrobenzyl esters, peptides and oligosaccharides); and

d) cleaving the cleavable linker (col. 12, lines 19-28).

With regard to claim 7, Summerton teaches an embodiment of claim 1, wherein the solid support portion comprises an insoluble synthetic polymer (col. 18, lines 54-56, where the microparticles comprise polystyrene).

With regard to claim 8, Summerton teaches an embodiment of claim 7, wherein the polymer is selected from polystyrene and polyacrylic polymers (col. 18, lines 54-56, where the microparticles comprise polystyrene).

With regard to claim 11, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase further comprises one or more connecting portions (col. 9, lines 38-42, where a spacer group or additional linkage groups can connect the capture component to the reagent surface).

With regard to claim 12, Summerton teaches an embodiment of claim 1, wherein the solid phase further comprises a magnetically responsive portion (col. 5, lines 13-60, where glass beads, or beads with polyethylene glycol linkages to reduce binding of undesirable components, and the use of magnetic particles are discussed; see also col. 18, lines 34-55).

With regard to claim 19, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved reductively (col. 9, lines 28-31, where the disulfide is cleaved with a sulfhydryl).

With regard to claim 20, Summerton teaches an embodiment of claim 19, wherein the cleavable linker comprises a disulfide group (col. 2, lines 41-43; see also col. 9, lines 28-31).

With regard to claim 21, Summerton teaches an embodiment of claim 19, wherein the reductive cleavage is performed with a reducing agent selected from thiols, amines and phosphines. (col. 9, lines 28-31, where the disulfide is cleaved with a sulfhydryl).

With regard to claim 22, Summerton teaches an embodiment of claim 21, wherein the reducing agent is selected from 2-mercaptoethanol or dithiothreitol (col. 9, lines 28-31).

With regard to claim 30, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved enzymatically (col. 9, lines 28-37, where the enzymes disclosed include esterases, peptidases, proteases, oligosaccharidases, glycosidases).

With regard to claim 32, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises an ester which is cleaved by hydrolase enzyme (col. 2, lines 41-45; see also col. 9, lines 28-37).

With regard to claim 33, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises an amide which is cleaved by a protease enzyme (col. 9, lines 28-37, where peptides are cleaved by peptidases or proteases).

With regard to claim 34, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises a peptide which is cleaved by a peptidase (col. 2, lines 41-45; see also col. 9, lines 28-37, where peptides are cleaved by peptidases or proteases).

With regard to claim 35, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises a glycoside which is cleaved by a glycosidase (col. 2, lines 41-45; see also col. 9, lines 28-37, where oligosaccharides are cleaved by glycosidases).

With regard to claim 42, Summerton teaches an embodiment of claim 1, wherein the cleaving and releasing steps are performed as sequential steps using separate and distinct solutions to accomplish each step (col. 5, lines 1-7, where non-target polynucleotides are released through cleavage of linkers, followed by elution of target molecules in a subsequent step).

With regard to claim 43, Summerton teaches an embodiment of claim 1, wherein the cleaving and releasing steps can be performed together in the same step (col. 6, lines 58-64, where a strongly basic amine is used in the capture component and bound molecules are released

by selective cleavage of the linkage instead of through elution with adjustments to pH of solutions).

With regard to claim 45, Summerton teaches an embodiment of claim 1, wherein the step of separating the sample from the solid phase is accomplished by magnetic separation (col. 18, lines 64 to col. 19, line 17, where magnetic separation was used in the isolation of poly-A tailed alpha globin RNA).

With regard to claim 46, Summerton teaches an embodiment of claim 1, wherein the step of separating the sample from the solid phase is accomplished by a process selected from centrifugation and vacuum aspiration (col. 19, lines 8-11, where supernatant was aspirated).

With regard to claim 50, Summerton teaches an embodiment of claim 48, wherein the solution containing the released nucleic acid is used directly in a nucleic acid amplification reaction whereby the amount of the nucleic acid or segment thereof is amplified using a polymerase or ligase-mediated reaction (col. 14, lines 16-24).

Regarding claim 1 and 3, neither Greenfield, Ishikawa or Summerton teach quaternary ammonium groups wherein R is selected from C4-C20 alkyl, aralkyl and aryl groups, or a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and where X is an anion. Warth teaches the formation of quaternary ammonium and phosphonium resins for anion-exchange chromatography.

With regard to claim 1, Warth teaches quaternary ammonium groups wherein R is selected from C4-C20 alkyl, aralkyl and aryl groups (p. 73, tributyl amine, TBA, see also Figure 1, p. 77-78), or a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20

alkyl, aralkyl and aryl groups, and where X is an anion (p. 73, tributylphosphine resin (TBP), see also Figure 1, p. 77-78).

With regard to claim 3, Warth in view of Greenfield teaches an embodiment of claim 1, wherein the nucleic acid binding portion is a quaternary ammonium group and the R groups each contain from 4-20 carbons (p. 73, tributyl amine, TBA, see also Figure 1, p. 77-78, where R is a butyl group).

With regard to claim 4, Warth in view of Greenfield teaches an embodiment of claim 1 wherein the solid phase is selected from a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl, and aryl groups, and wherein X is an anion (p. 73, tributylphosphine resin (TBP), see also Figure 1, p. 77-78, where R is a butyl group).

With regard to claim 5, Warth teaches an embodiment of claim 4, wherein each R group of the solid phase is a butyl group (p. 73, tributylphosphine resin (TBP), see also Figure 1, p. 77-78, wherein each R group is a butyl group).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the cleavable linker formats taught by Summerton into the isolation technique taught by Greenfield. Greenfield teaches, "Nucleic acid binding components can be attached to other components of the solid substrate by any method or linkage known in the art" (p. 7, paragraph 97). Greenfield also teaches "a binding unit can also be a physically or functionally distinct quantity of the solid substrate that is part of an array, where the binding units in the array can simultaneously contact a single sample solution of a nucleic acid, where after the contacting, the individual binding units are conveniently separable from each other at predetermined separation points. For instance, the binding units could be polyhedrons connected

in an array by linkers, where the polyhedrons can be conveniently separated from the linkers at predetermined points" (p. 2, paragraph 32). While this teaching indicates Greenfield teaches the inclusion of linkers together with solid supports, separation of the linkers, and the inclusion of a any linkages known in the art between the nucleic acid binding unit and the solid support, Greenfield does not explicitly teach the inclusion of a cleavable linker or cleavage of the linker.

Summerton teaches a method that comprises the inclusion of a linkage that is cleavable. Specifically, Summerton teaches "a solid or porous surface to which is linked a capture component preferably by a cleavable linker" and "the non-specific capture component is effective to rapidly and non-specifically bind polynucleotide molecules, and is designed such that polynucleotides can be released from this component" (col. 4, lines 36-43). Summerton also teaches that the nucleic acids bound "are selectively released from the capture component following probe-target pairing, preferably via cleavage of linkers" (col. 5, lines 1-4). Additionally, it is noted that Summerton provides a cleavable linkage between a non-specific binding component and the solid support and Greenfield teaches that the non-specific nucleic acid binding units can be connected to the solid support by any type of linkage. The cleavable linkage provided by Summerton therefore provides an additional method of selectively releasing the bound nucleic acids without elution using buffers as presently disclosed by Greenfield.

Considering that Greenfield is directed to obtaining nucleic acids from biological samples through binding to a non-specific nucleic acid binding component and to the selective binding and/or elution of nucleic acids and also teaches the inclusion of a linker in certain embodiments of the invention, the inclusion of the cleavable linker provided by Summerton provides for selective release of polynucleotides which bind non-specifically to the capture component.

Based on the ability to cleave and release nucleic acids bound non-specifically to the solid support through the cleavable linkages taught by Summerton and considering the specific formats of cleavable linkages taught by Summerton for elution of non-sequence specifically bound nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the cleavable linkers taught by Summerton into the method of isolation taught by Greenfield to achieve additional methods of selective release of nucleic acids with a reasonable expectation for success.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Greenfield and Summerton to include the anion exchange resins of Warth to arrive at the claimed invention with a reasonable expectation for success. As taught by Warth, the study was to "evaluate and compare the selectivity and performance of low-capacity quaternary phosphonium and ammonium resins in anion chromatography". While Warth does not apply these resins to the binding or elution of nucleic acids or other biological molecules and instead focuses on establishing "the relative retention times of various anions", the resins would be applicable to other formats where solid phase resins would be useful, including as part of the combined teachings of Greenfield and Summerton. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Greenfield and Summerton to include the anion exchange resins of Warth to arrive at the claimed invention with a reasonable expectation for success.

2. Claim 13-15, 23-29, 51-52 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (US PgPub 2004/0121336; June 2004) as evidenced by Ishikawa et al. (Colloid and Polymer Science, 1984, vol. 262, p. 477-480) in view of Summerton et al. (US Patent 6,060,246; May 2000) and Warth, Linda (Thesis, UMI, Iowa State University, 1988, p. 70-102, 144-146, 'Warth' herein) and as applied to claims 1, 3-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Schaap et al. (US Patent 5,707,559; January 1998). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

With regard to claim 51, Greenfield teaches a method of isolating a nucleic acid from a sample comprising:

a) providing a solid phase comprising a matrix selected from silica, glass, insoluble synthetic polymers, and insoluble polysaccharides (p. 2, paragraph 31, where the support can comprise silica, beads or resin); a nucleic acid binding portion for attracting and non-sequence-specific binding of nucleic acids, wherein the nucleic acid binding portion of the solid phase is selected from a ternary sulfonium group of the formula SR2+X- where R is selected from C1-C20 alkyl, aralkyl and aryl groups, a quaternary ammonium group of formula NR3+X- wherein R is selected from alkyl, aralkyl and aryl groups, and a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and where X is an anion (p. 3, paragraph 31, where the binding component may comprise anion exchange groups such as DEAE or p. 3, paragraph 42, where the anion exchange group refers to tertiary and quaternary amines or see p. 6, paragraph 75, where the exchange resins include QAE , a quaternary ammonium group, referring specifically to diethyl(2-hydroxypropyl)aminoethyl as evidenced by

Ishikawa, p. 477, 'materials and methods'; see also p. 6, paragraph 77, where the binding units can comprise tetramethyl ammonium, tetraethyl ammonium, tetrapropyl ammonium, tetrabutyl ammonium and combinations therein, where these also represent quaternary ammonium groups together with a variety of anions, including chloride and fluoride);

b) combining the solid phase with the sample containing the nucleic acid to bind the nucleic acid to the solid phase (p. 6, paragraph 71, where nucleic acids are bound to the binding units);

c) separating the sample from the solid phase and e) releasing the nucleic acid from the solid phase (p. 6, paragraph 79, where after binding the units are washed and therefore are separated from the original sample and paragraph 71, where the nucleic acids are eluted before being used in an assay).

d) a linker portion linking the nucleic acid binding portion to the solid support (p. 7, paragraph 97; p. 2 paragraph 32).

Regarding claim 51, Greenfield does not teach the limitation that the solid phase comprises a cleavable linker portion or cleaving the cleavable linker portion.

Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

With regard to claim 51, Summerton teaches a cleavable linker portion linking the nucleic acid binding portion to the solid support (col. 7, lines 15-17 and col. 8, line 64 to col. Col. 9, line 42, where the cleavable linker can include disulfide, esters, orthonitrobenzyl esters, peptides and oligosaccharides); and

d) cleaving the cleavable linker (col. 12, lines 19-28).

With regard to claim 54, Summerton teaches a embodiment of claim 51, wherein the solution containing the released nucleic acid is used directly in a nucleic acid amplification reaction whereby the amount of the nucleic acid or segment thereof is amplified using a polymerase or ligase-mediated reaction (col. 14, lines 16-24).

Regarding claim 51, neither Greenfield or Summerton teach quaternary ammonium groups wherein R is selected from C4-C20 alkyl, aralkyl and aryl groups, or a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and where X is an anion. Warth teaches the formation of quaternary ammonium and phosphonium resins for anion-exchange chromatography.

With regard to claim 1, Warth teaches quaternary ammonium groups wherein R is selected from C4-C20 alkyl, aralkyl and aryl groups (p. 73, tributyl amine, TBA, see also Figure 1, p. 77-78), or a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and where X is an anion (p. 73, tributylphosphine resin (TBP), see also Figure 1, p. 77-78, where R is a butyl group).

Further regarding claim 51, Summerton does not teach that the linker is cleaved by hydrolysis and does not explicitly teach the inclusion of dioxetane linkages as a part of the invention disclosed as recited in the 102 rejection stated above, but Summerton does teach the inclusion of cleavable linkages of a variety of forms in the isolation of target nucleic acids. Schaap teaches novel light-producing compounds termed 1,2-dioxetanes which can be triggered to produce light at room temperature (Abstract).

With regard to claim 13 and 51, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved hydrolytically (col. 26, lines 54-65, where

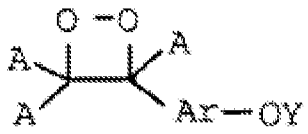
the base is potassium hydroxide; col. 27, lines 44-46, where the proof of enzyme-catalyzed hydrolysis begins).

With regard to claim 14 and 51, Schaap teaches an embodiment of claim 13, wherein the hydrolytic cleavage is performed with a solution that contains a base selected from hydroxide and alkoxide salts (col. 26, lines 54-65, where the base is potassium hydroxide).

With regard to claim 15 and 52, Schaap teaches an embodiment of claim 14, wherein the base is selected from hydroxide salts and alkoxide salts (col. 26, lines 54-65, where the base is potassium hydroxide).

With regard to claim 23, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase comprises a triggerable dioxetane ring which is cleaved by a triggering agent (Abstract, see also col. 26, lines 40-65).

With regard to claim 24, Schaap teaches an embodiment of claim 23, wherein the triggerable dioxetane has the formula



wherein the group A represent stabilizing substituents selected from alkyl, cycloalkyl, aryl, aryloxy, and alkoxy (col. 6, lines 43-65, where A, or R1, R3 and R4, is selected from alkyl, alkoxy, aryloxy, and spirofused aryl groups), Ar represents an aryl ring group which can contain additional substituents selected from halogens, alkoxy and amine groups (col. 6, lines 43-65, where R2 is an aryl which can include oxy groups), Y is a group or atom which is removable by a triggering agent selected from the chemical agents and enzymes to cause fragmentation of the dioxetane ring (col. 6, line 43 to col. 7, line 25, wherein OY is an oxy group substituted on an

aryl ring which forms an unstable oxide intermediate 1,2-dioxetane compound when triggered to remove Y by an activating agent).

With regard to claim 25, Schaap teaches an embodiment of claim 24, wherein the OY group is selected from OH, $OSiR^3{}_3$, wherein R^3 is selected from alkyl and aryl groups, carboxyl groups, phosphate salts sulfate salts and glycoside groups (col. 8, lines 3-12, where OY can be hydroxyl, aryl siloxy and oxygen pyranoside, for example).

With regard to claim 26, Schaap teaches an embodiment of claim 24, wherein Ar in the triggerable dioxetane is a substituted or unsubstituted phenyl or napthyl group (col. 8, lines 3-12, where Ar or R2 is an aryl group that can be a phenyl, biphenyl, fused phenyl and other aryl groups that can contain between 6 and 30 carbon atoms and can include other substituents).

With regard to claim 27, Schaap teaches an embodiment of claim 23, wherein the triggering agent is selected from bases, fluoride ion, a esterase, a phosphatase, a sulfatase, and a glycosidase (col. 26, lines 40- col. 27, lines 28-66, where the triggering agent is selected from bases, fluoride ion and see col. 40; see also col. 8, lines 28-39, where additional triggering agents acids, bases, salts and enymes).

With regard to claim 28, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase comprises an electron rich alkene, which is cleaved by conversion to a thermally unstable dioxetane (col. 8, lines 49-67).

With regard to claim 29, Schaap teaches an embodiment of claim 28, wherein the alkene is converted to the unstable dioxetane by reaction with a singlet oxygen (col. 8, lines 49-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the dioxetane compound taught by Schaap into the DNA

binding compound which incorporated cleavable linkers in the isolation of target nucleic acid molecules as taught by a combination of Greenfield, Summerton and Warth. As taught by Schaap, the dioxetane compound is a "novel stable 1,2-dioxetanes which can be decomposed with an activating agent to form light and two carbonyl compounds" and furthermore, a compound that is stable at room temperature for an extended period of time, that is activatable by chemical and biochemical means, and which can generate light (col. 5, lines 22-34). At the time the invention of Schaap was made, dioxetane compounds were known to be capable of chemiluminescence, but the compounds were unstable or needed to be reacted under conditions unfavorable to evaluation of biological macromolecules (col. 1-3). With the improvements made with the synthesis of the compound taught by Schaap, the dioxetane compound provides a stable compound, capable of being cleaved by enzymatic or chemical means and yields stable fluorescence. The target nucleic acid isolation technique taught by Summerton has an embodiment directed to the isolation of non-specific and specific target nucleic acids. Summerton teaches the use of multiple types of linkers to connect the different capture portions of the solid phase and it would have been obvious to include another variation, particularly one as versatile as the dioxetane compound taught by Schaap. One of ordinary skill in the art would have recognized the benefit of luminescence upon cleavage of a cleavable linkage used in the isolation of nucleic acids, and the additional benefits of a thermally stable chemical linkage capable of enzymatic or chemical cleavage. Luminescence upon cleavage would have provided an additional method of detecting cleavage of the non-specifically bound nucleic acids from the capture agent, and would have provided an additional method for detection and analysis of the released nucleic acids. Therefore one of ordinary skill would therefore have been motivated to

incorporate the dioxetane compound as an additional type of cleavable linker, in addition to those specifically taught by Summerton, with a reasonable expectation of success.

3. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (US PgPub 2004/0121336; June 2004) as evidenced by Ishikawa et al. (Colloid and Polymer Science, 1984, vol. 262, p. 477-480) in view of Summerton and Warth, Linda (Thesis, UMI, Iowa State University, 1988, p. 70-102, 144-146, 'Warth' herein) as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Singh et al. (US Patent 6,514,700; February 2003). Greenfield in view of Summerton and Warth teach the limitations of claims 1, 3-12, 19-22, 30, 32-35, 42-46 and 48-50 as recited in the 103 rejection stated above. Neither Summerton or Greenfield teaches hydrolytic cleavage in a solution that contains hydrogen peroxide.

Regarding claim 16, Singh teaches a method wherein the hydrolytic cleavage is performed with a solution that also contains hydrogen peroxide (col. 9, lines 26-37, where hydrogen peroxide is used in oxidative cleavage of the linker).

Regarding claim 17, Singh teaches a method wherein the hydrolytic cleavage is performed with a solution that contains a mineral acid (col. 9, lines 10-15, where HCl is included in a cleavage reaction).

It would have been prima facie obvious to one of ordinary skill in the art to substitute hydrogen peroxide and mineral acid for the base or enzymatic cleavage taught by Summerton. It is standard in the art to adjust reaction conditions to achieve the most efficient combination of solvents or reagents appropriate to the specific experiment being conducted. As taught by Singh,

there are multiple options for cleavage of a linkage, including, but not limited to "silyl groups being cleaved with fluoride, oxidation, acid bromine or chlorine; o-nitrobenzyl with light; catchecols with cerium salts; sulfides with singlet oxygen or enzyme catalyzed cleavage with hydrogen peroxide" (col. 9, lines 26-37). One of ordinary skill in the art would have recognized the role that routine optimization and substitution of reagents play in the art, who would therefore have been motivated to substitute hydrogen peroxide for the other types of linkages and cleavage options previously taught by Summerton, with a reasonable expectation of success.

4. Claims 18, 36-37, 41 and 53are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (US PgPub 2004/0121336; June 2004) as evidenced by Ishikawa et al. (Colloid and Polymer Science, 1984, vol. 262, p. 477-480) in view of Summerton, Warth and Schaap as applied to claims 13-15, 23-29, 51-52 and 54 above and further in view of Mukhamedgaliev et al. (1994, Uzbekskii Khimicheskii Zhurnal (6), p. 41-3, citations in rejection refer to attached English translation of Russian document) and further in view of Reinecke et al. (Macromol. Rapid Commun., 1996, vol. 17, no. 15-23) and further in view of Bronstein et al. (US Patent 6,602,657; August 2003) and further in view of Goshe et al. (US Patent 6,818,454; November 2004). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

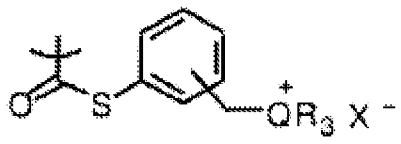
Summerton does not explicitly teach the inclusion of a quaternary phosphonium group as part of the nucleic acid binding portion of their invention, nor does Summerton teach linkage of the phosphonium group to a resin via a thioester linkage as displayed below. With regard to claim 18 and 53, Mukhamedgaliev teaches the formation of quaternary phosphonium groups

following reaction between methacrylol chloride and triphenylphosphine (p. 1, paragraphs 1-3, where methacryloyl chloride (MAC) was reacted with tri-phenyl phosphine (TPP) and p. 2, bottom paragraph, a polymer that contains quaternary phosphonium groups is formed), which anticipates key components of the formation of the thioester recited in claims 36 and 37 as recited in Example 14 (p. 17 of the specification).

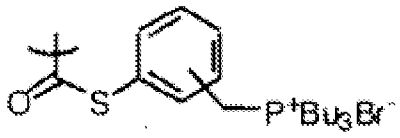
Mukhamedgaliev however, does not explicitly teach the structure of the compound synthesized or the attachment to the polymer using a thioester linkage.

Reinecke teaches a step that would anticipate the step of reacting the resin with 2-mercaptobenyl alcohol as exemplified in Example 14, that is missing from Mukhamedgaliev (Abstract).

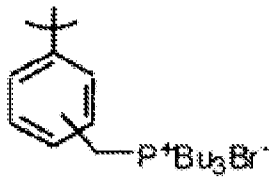
With regard to claim 36, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



With regard to claim 37, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



With regard to claim 41, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the various teachings in the art at the time the invention was made, to modify a standard resin to attach a phosphonium group via a thioester linkage. As taught by Reinecke, the use of 2-mercaptobenzyl alcohol, or other aromatic thiols are useful in multi-step reactions, such as the PVC crosslinking analysis taught by Reinecke, because "aromatic thiols can easily substitute chlorine atoms in PVC under Sn2 mechanism, either in solution or melt conditions" and goes on to note further benefits of this type of reaction, including that there are no side reactions due to the high nucleophilicity and low basicity of sulfur (p. 15, paragraph 3). The benefit of a resin with a phosphonium group attached has been established by previously noted references, including the teaching of the relative equivalence between phosphonium, ammonium and sulfonium groups by Bronstein (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19) and the teaching by Goshe that the inclusion of an ammonium or phosphonium group within the support provides a binding group that maintains its charge (col. 9, lines 59-62). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the separate teachings of Summerton, Mukhamedgaliev and

Reinecke to arrive at a resin with a phosphonium group attached via a thioester linkage with a reasonable expectation of success.

5. Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (US PgPub 2004/0121336; June 2004) as evidenced by Ishikawa et al. (Colloid and Polymer Science, 1984, vol. 262, p. 477-480) in view of Summerton and Warth as applied to claims 1, 3-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Hughes et al. (Tetrahedron Letters, 1996, vol. 37, no. 42, p. 7595-7598) and Hagashita et al. (US Patent 4,904,819; February 1999). Greenfield in view of Summerton teaches the limitations of claims 1-3, 6-10, 12, 19-22, 30, 32-35, 42-46 and 48-50 as recited in the 103 rejection stated above. However, neither Greenfield or Summerton teach a linkage to the solid phase which is an alkylene group bonded to a trivalent phosphonium group, such as trialkylphosnium or triarylphosphonium.

With regard to claim 38, Hughes in view of Summerton teaches an embodiment wherein the cleavable linker portion of the solid phase is an alkylene group of at least one carbon atom bonded to a trialkylphosphonium or triarylphosphonium, nucleic acid binding position and is cleavable by means of a Wittig reaction with a ketone or aldehyde (p. 7596, bottom paragraph, where the Wittig cleavage of the phosphonium salt to stilbene is described). Hughes does not teach the intricate details of the Wittig reaction as recited in claims 39 and 40. Hagashita teaches the use of a Wittig reaction in the synthesis of bicyclic sulfonamide derivatives (Abstract).

With regard to claim 39, Hagashita teaches an embodiment of claim 38, wherein the Wittig reaction forms a ylide by deprotonation with an alkoxide salt or hydride salt base in an

aprotic organic solvent and the ylide reacts with a carbonyl compound selected from aliphatic and aromatic aldehydes and aliphatic and aromatic ketones (col. 6, lines 29-62, where the base treatment includes sodium hydride).

With regard to claim 40, Hagashita teaches an embodiment of claim 39, wherein the solvent is selected from THF, diethyl ether, p-dioxane, DMF and DMSO and the carbonyl compound for reaction with the ylide is acetone (col. 6, line 29 to col. 7, line 15, where tetrahydrofuran or dimethylformamide were noted as a potential solvents and acetone were noted).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teachings in the art of the inclusion of triphenylphosphine containing compounds attached to a resin, as exemplified by Hughes. As taught by Hughes, "The Wittig reaction of polymer-bound phosphonium salts has been reviewed and has a key advantage that the phosphine oxide by-product remains bound to the polymer and is thus easily separated from the soluble olefinic product by filtration" (p. p. 7595-7596). Hughes also notes that "readily available polymer-supported phosphonium salts can be elaborated with reagents including strong acids, organic bases and reducing agents, and can be cleaved under basic conditions to products lacking polar functionality. The phosphonium linkage thus complements many existing linkers both in its acid/base stability profile and its cleavage products. This phosphonium linker is currently being exploited for the solid phase synthesis of combinatorial libraries (p. 7597, bottom). The versatility of the triphenyl phosphine compound in reductive reactions would have been obvious to one of ordinary skill in the art who would therefore have

been motivated to include the triphenyl phosphine group into the solid phase binding of nucleic acids taught by Summerton with a reasonable expectation of success.

6. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (US PgPub 2004/0121336; June 2004) as evidenced by Ishikawa et al. (Colloid and Polymer Science, 1984, vol. 262, p. 477-480) in view of Summerton et al. (US Patent 6,060,246; May 2000) and Warth as applied to claim 1, 3-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Bronstein et al. (US Patent 6,602,657; August 2003) and further in view of Goshe et al. (US Patent 6,818,454; November 2004). Greenfield in view of Summerton teaches the limitations of claims 1, 3-12, 19-22, 30, 32-35, 42-46 and 48-50 as recited in the 103 rejection stated above. Neither Greenfield, Summerton or Warth teach of the use of ternary sulfonium groups for binding of nucleic acids, however amine groups are discussed.

In addition to the quaternary ammonium taught by Greenfield, Bronstein teaches a method of measuring the activity of at least two reporter gene products, including a water soluble polymeric enhancer molecule to enhance the light signal (Abstract, col. 4, lines 5-20).

With regard to claim 47, Bronstein teaches an embodiment of claim 1, wherein the nucleic acid binding portion of the solid phase is a ternary sulfonium group of the formula SR2+X- where R is selected from C1-C20 alkyl, aralkyl and aryl groups, and wherein X is an anion (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19, where the polymeric structures include sulfonium salts; and where the R group contain a 1-20 carbons).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute a ternary sulfonium group for the quaternary ammonium group taught by Greenfield and Warth. As taught by Bronstein, the inclusion of an ammonium or

phosphonium groups as part of synthetic oligomeric or polymeric enhancer substances (col. 11, 63-66), in the method taught by Bronstein "enhances the light signal produced by enzymatic degradation of the dioxetane" (col. 4, lines 5-8). While Bronstein does not teach the inclusion of these groups in the binding of nucleic acids, Brontein does teach an equivalence between quaternary onium groups, including ammonium, phosphonium and sulfonium. Further, as taught by Goshe, ammonium, phosphonium or sulfonium groups retain their charge (col. 9, lines 59-62). The maintenance of the charge of these groups allows for these groups to have non-specific affinity for nucleic acids in solution. The benefit of improved affinity for nucleic acids to a particular solid phase would have been obvious to one of ordinary skill in the art who would therefore have been motivated to include a phosphonium or sulfonium group where quaternary ammonium groups have been used in the past with a reasonable expectation of success.

Response to Arguments

Applicant's arguments with respect to claims 1, 3-43 and 45-54 have been considered but are moot in view of the new ground(s) of rejection.

Insofar as the arguments apply to the present rejections, in view of the newly cited, Harth reference, the rejections will be addressed.

Regarding the rejection over claims 1-3, etc. Applicant argues persuasively regarding the lack of specific teaching of a quaternary ammonium group comprising an alkyl group with 4 or more carbons. Regarding the amplification limitation of claims 48 and 50, Applicant's

arguments are noted (p. 15). However, amplification of nucleic acids attached to a solid phase has been achieved and Applicant's arguments are not persuasive.

Regarding the rejection of claims over Summerton, Greenfield and further in view of Schaap, Applicant asserts that the reference does not teach the use of dioxetanes as linkers. Summerton is relied upon for a teaching of the cleavable linker format. Applicant's arguments regarding the lack of alleged motivation are also not persuasive. Applicant is arguing the features of Schaap without the context of the additional references or the methods they teach. The method requires the nucleic acid is bound prior to cleavage of the linker, so the cleavage of the linker and the associated fluorescence would be indicative of achieving the final step in the method. The rejection is maintained.

Regarding the request for English translation of the Mukhamedgaliev reference (p. 18 of remarks), it is noted that an English translation was provided on September 25, 2006. An additional copy of this translation will be included with this office communication.

Conclusion

Claim 31 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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